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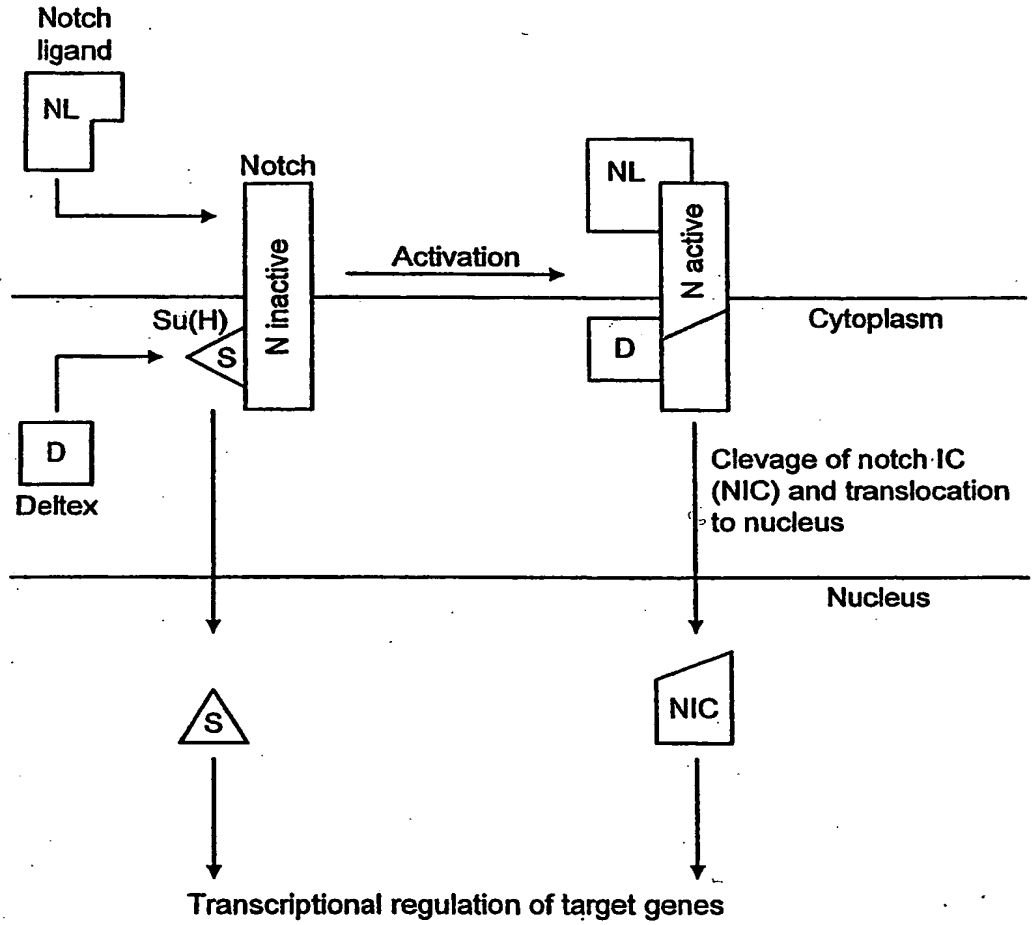

Notch ligand
NL
Notch
N inactive
Activation
NL
N active
Su(H)
S
Cytoplasm
D
D
Deltex
Clevage of notch IC (NIC) and translocation to nucleus
Nucleus
S
NIC
Transcriptional regulation of target genes

FIG. 1

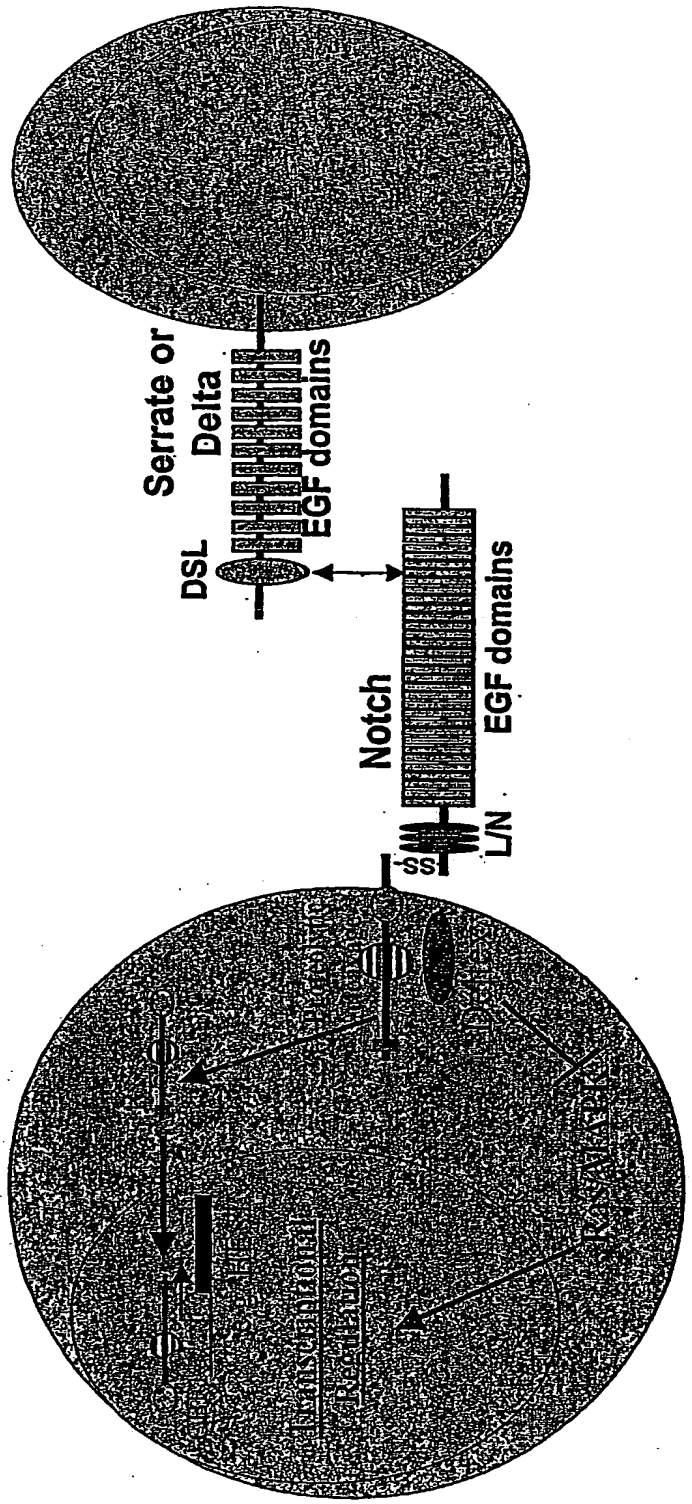

Serrate or
Delta
DSL
EGF domains
Notch
EGF domains
L/N
S2
S3
TRANSCRIPTION
ACTIVATION

Figure 2

FIGURE 3

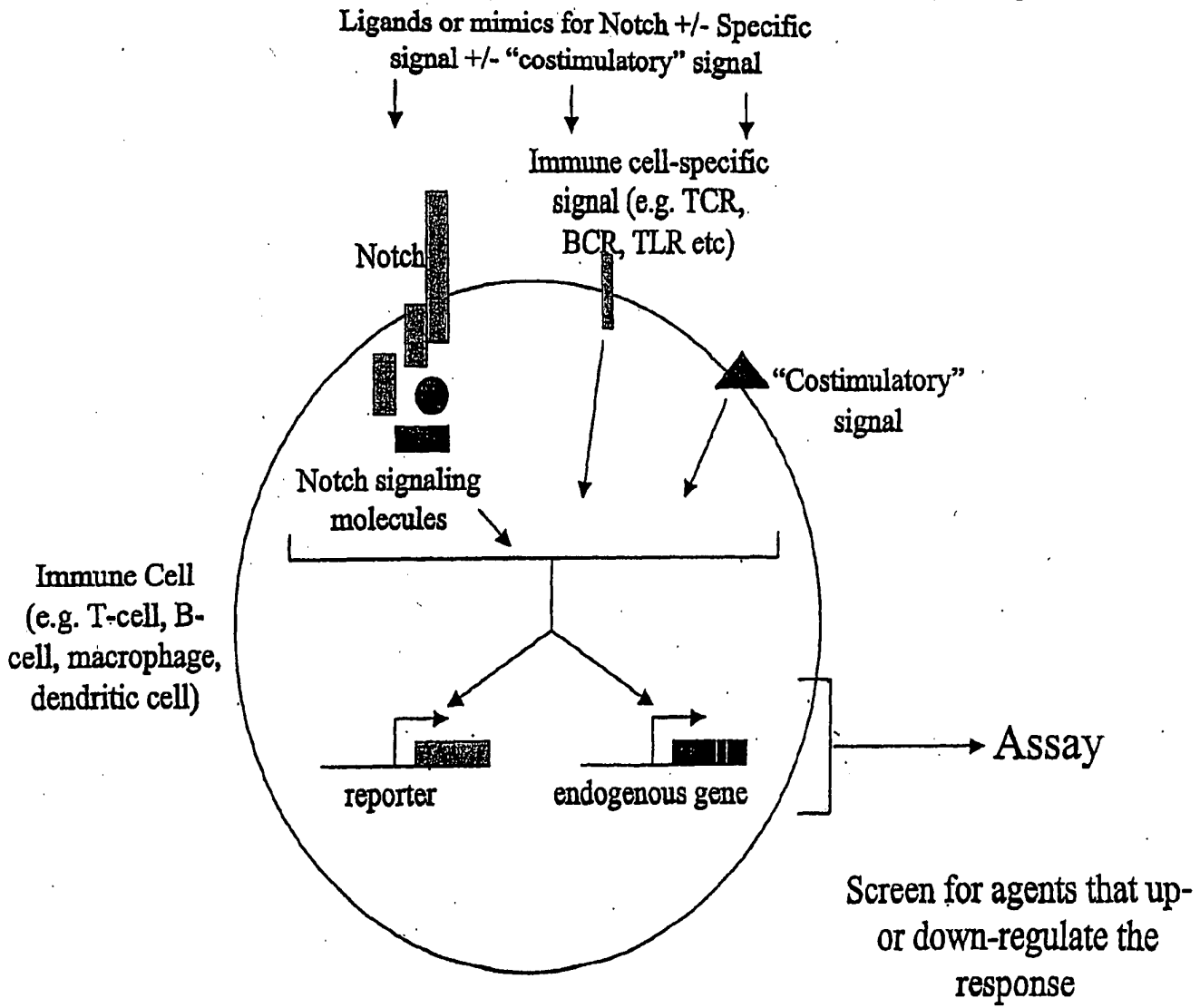

Ligands or mimics for Notch +/- Specific signal +/- "costimulatory" signal
Immune cell-specific signal (e.g. TCR, BCR, TLR etc)
Notch
"Costimulatory" signal
Notch signaling molecules
Immune Cell (e.g. T-cell, B-cell, macrophage, dendritic cell)
reporter
endogenous gene
Assay
Screen for agents that up- or down-regulate the response

Figure 4

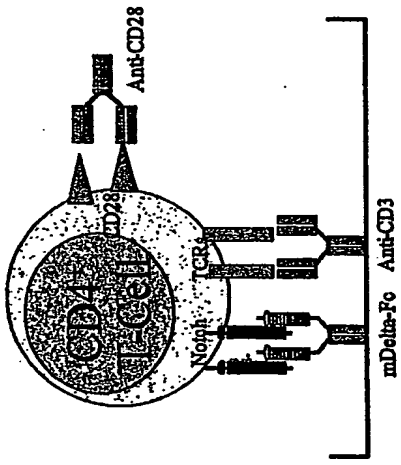


Figure 5

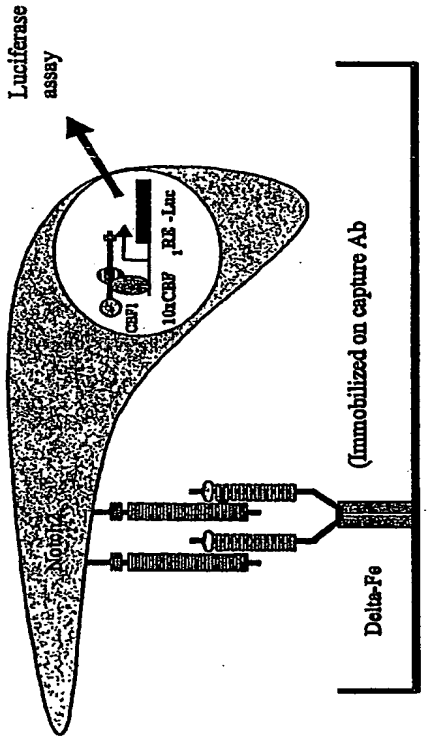

Luciferase assay
CBF1
10xCBF
RE -Luc
Notch
(Immobilized on capture Ab
Delta-Fc

Figure 6

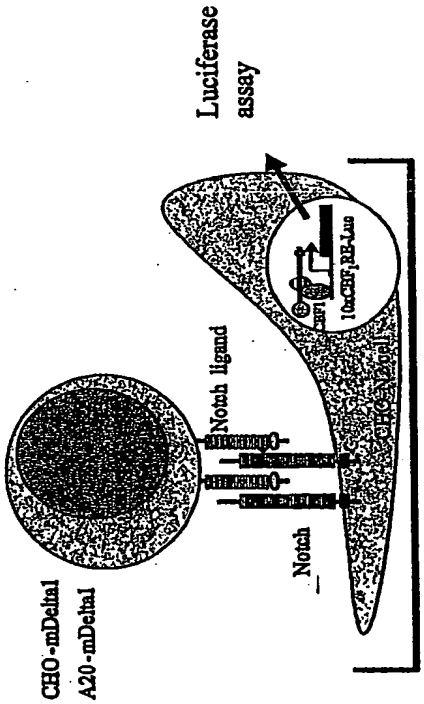

Luciferase assay
Notch ligand
Notch
CHO-mDelta1
A20-mDelta1
10xCBF1-RBP-Luc

Figure 7

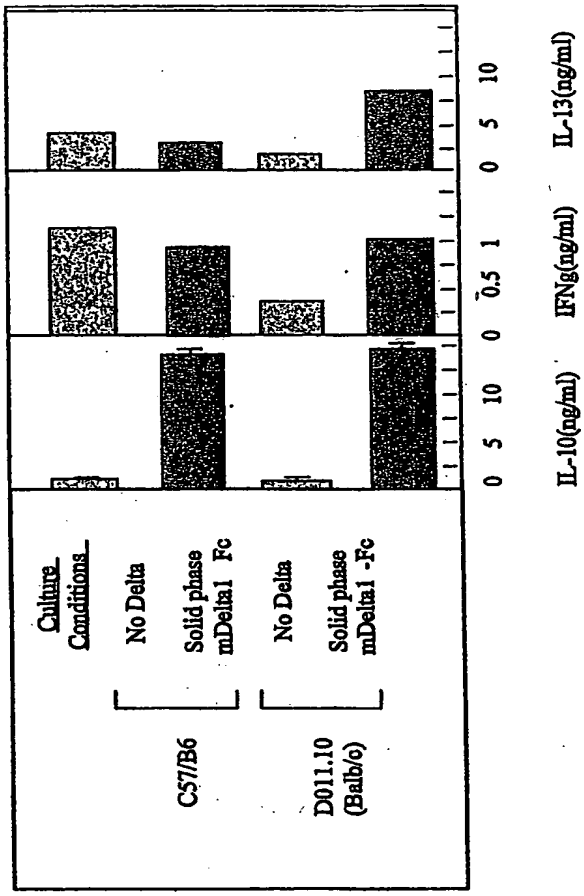

Culture Conditions
No Delta
Solid phase mDelta1 Fc
No Delta
Solid phase mDelta1 -Fc
C57/B6
D011.10 (Balb/c)
0 5 10
0 0,5 1
0 5 10
IL-10(ng/ml)
IFNg(ng/ml)
IL-13(ng/ml)

Figure 8

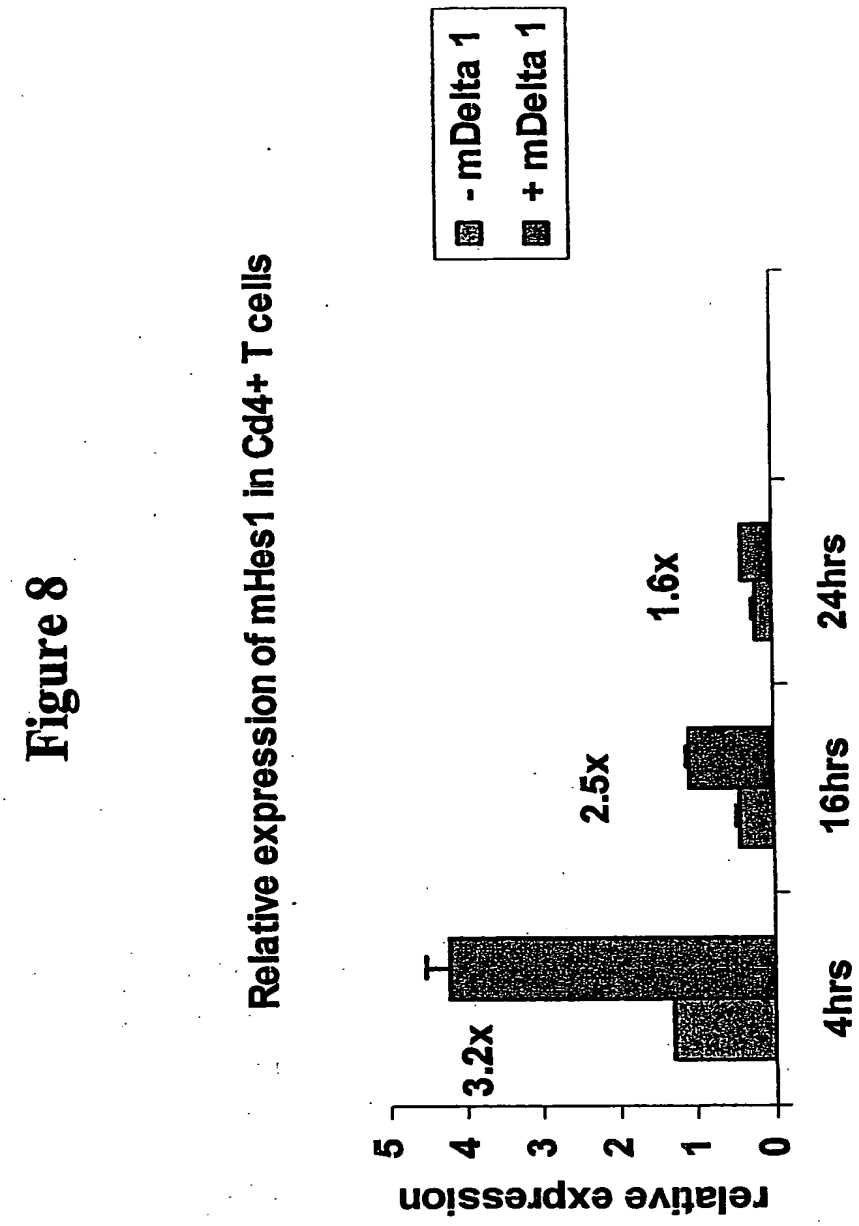

Relative expression of mHes1 in Cd4+ T cells
- mDelta 1
+ mDelta 1
relative expression
0
1
2
3
4
5
3.2x
2.5x
1.6x
4hrs
16hrs
24hrs

Figure 9

Cytokine production under polarising conditions

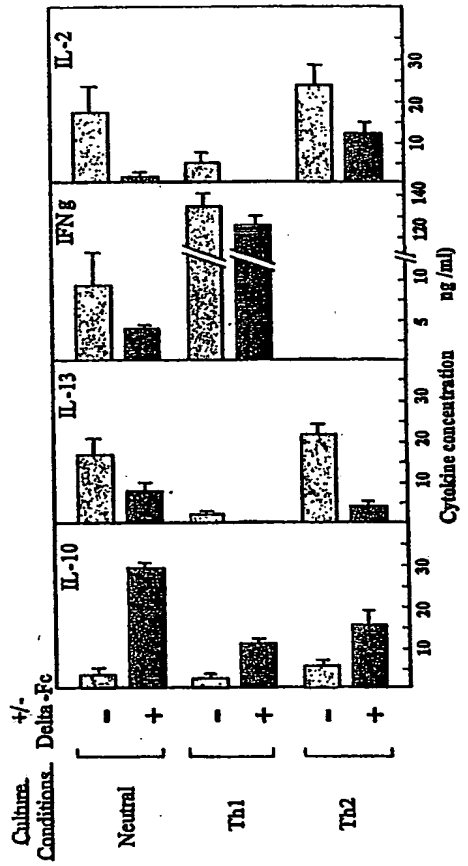


Figure 10

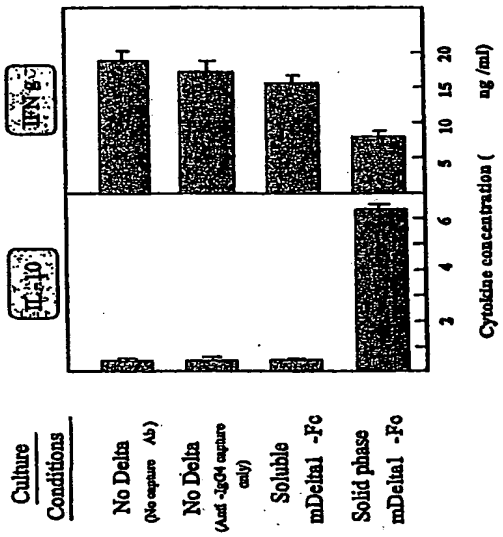

Culture Conditions
No Delta (No capture Ab)
No Delta (Anti -IgG4 capture only)
Soluble mDelta1 -Fc
Solid phase mDelta1 -Fc
IL-10
IFN-γ
2 4 6 5 10 15 20
Cytokine concentration (ng /ml)

Figure 11

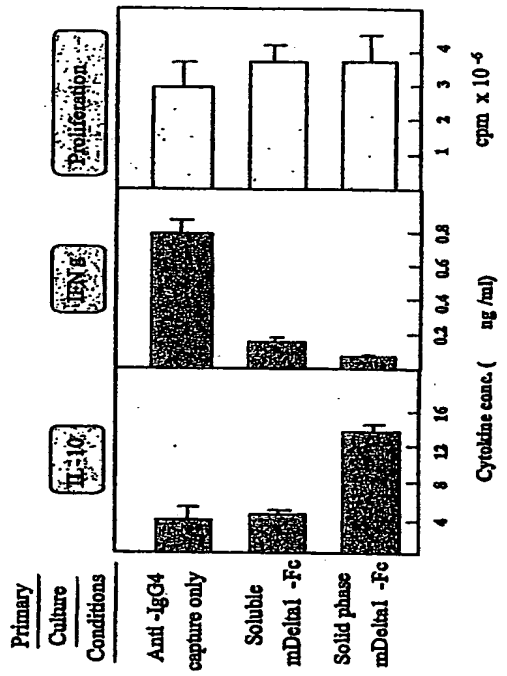

Primary Culture Conditions
IL-10
IFN g
Proliferation
Anti -IgG4 capture only
Soluble mDelta1 -Fc
Solid phase mDelta1 -Fc
4 8 12 16
0.2 0.4 0.6 0.8
1 2 3 4
Cytokine conc. (ng /ml)
cpm x 10⁻⁶

Figure 12

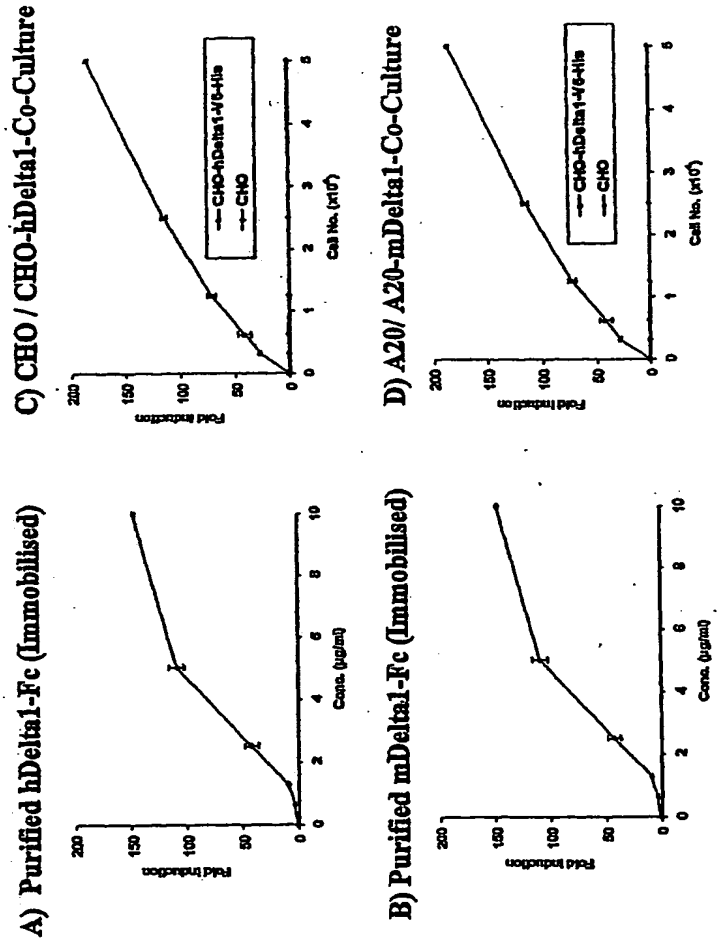
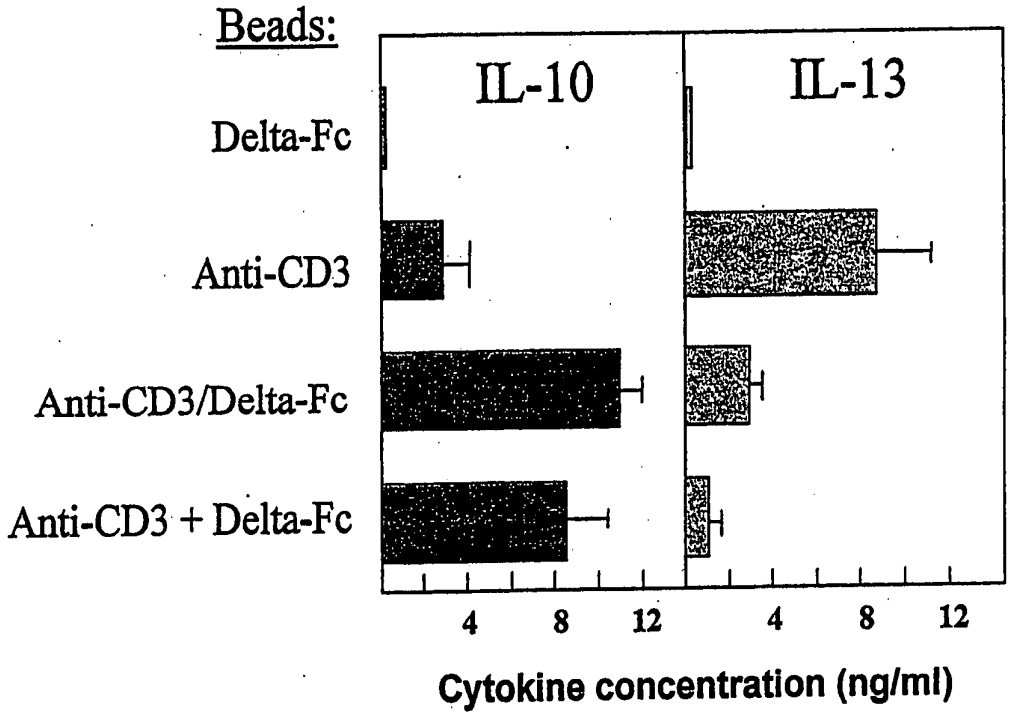

A) Purified hDelta1-Fc (Immobilised)
B) Purified mDelta1-Fc (Immobilised)
C) CHO / CHO-hDelta1-Co-Culture
D) A20/ A20-mDelta1-Co-Culture
Fold Induction
Conc. (µg/ml)
Cell No. (x10⁵)
CHO-hDelta1-V5-His
CHO

Figure 13: Delta-Fc coated beads modulate *in vitro* T-cell responses



CD4+ T-cells activated with beads coated as described plus soluble anti-CD28, 3d

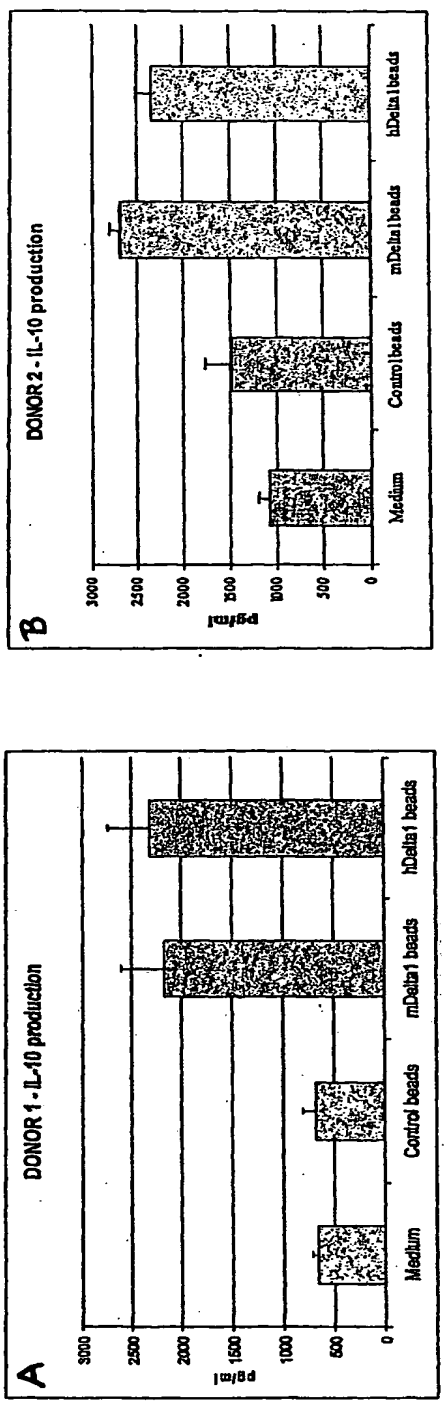


Figure 14: Increase in IL-10 production in the presence of mouse or human Delta1 beads

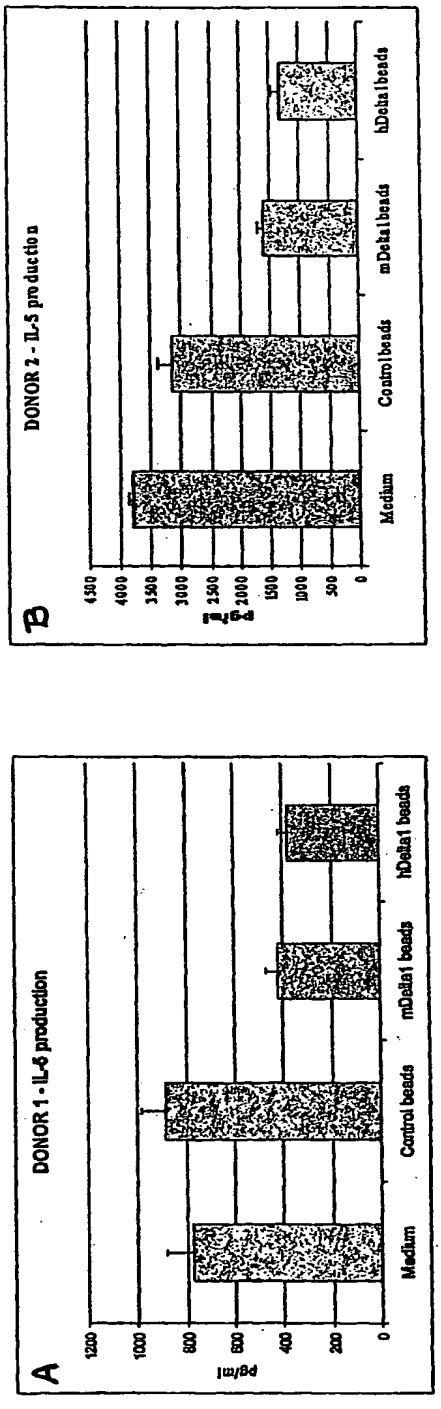


Figure 15: Decrease in IL-5 production in the presence of mouse or human Delta1 beads

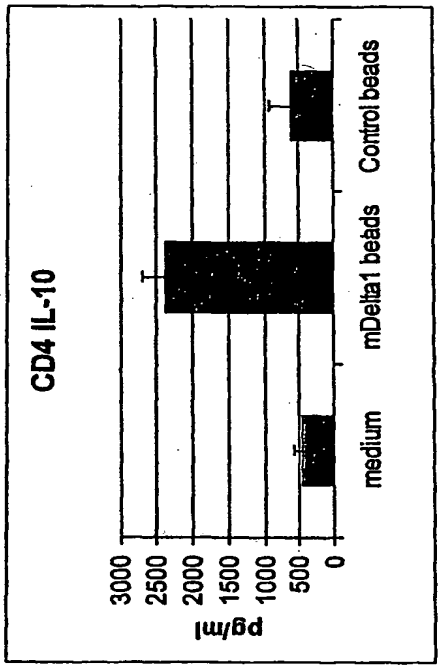


Figure 16: Increase in IL-10 production in the presence of mouse Delta1 beads

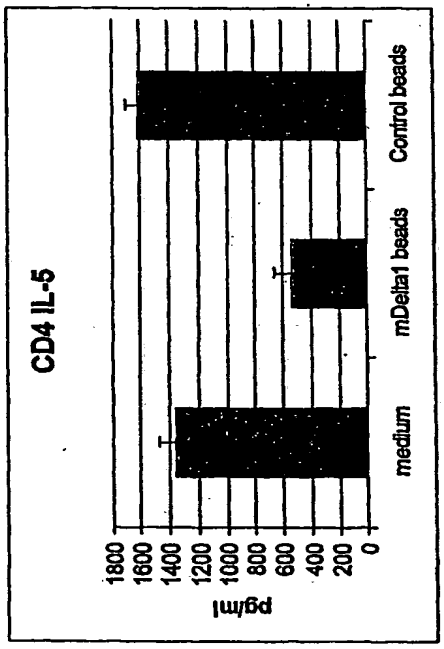
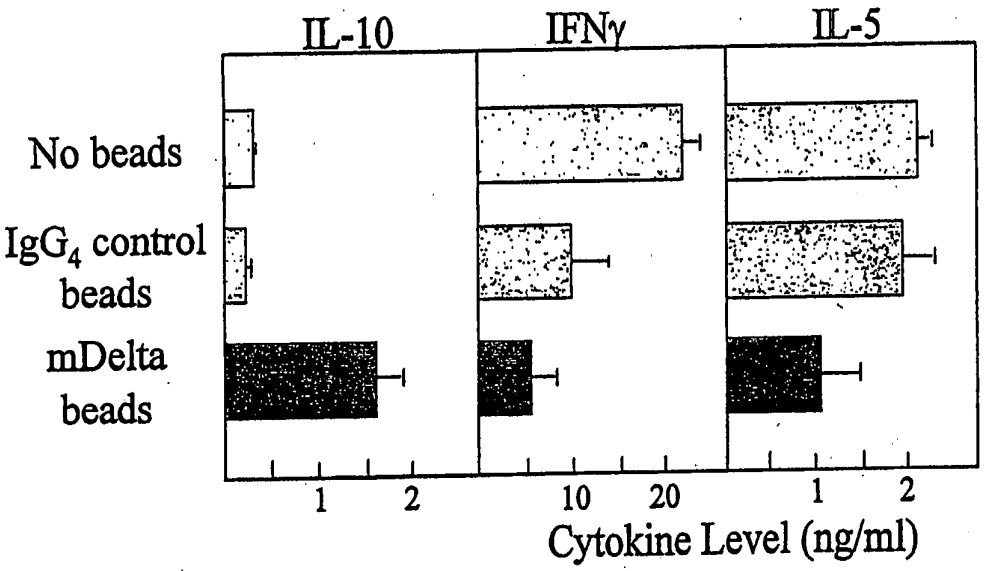


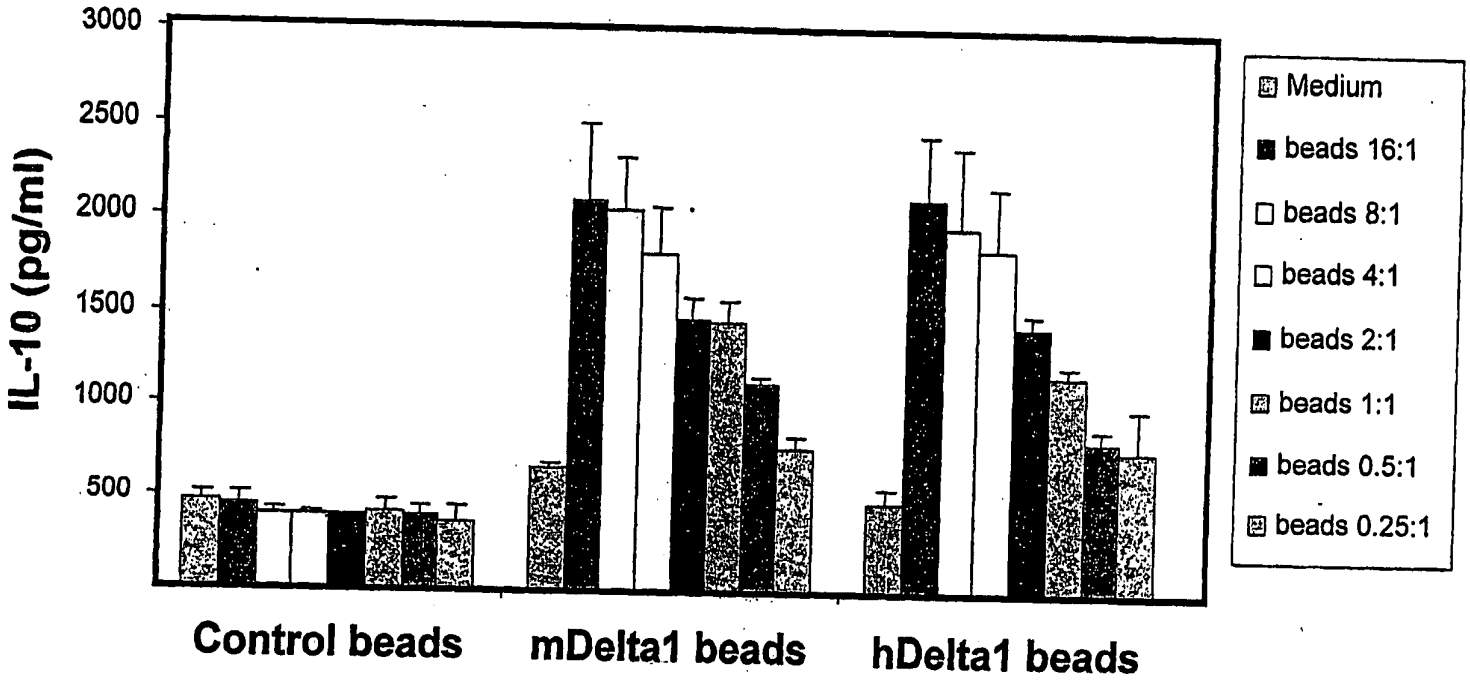
Figure 17: Decrease in IL-5 production in the presence of mouse Delta1 beads

Figure 18: mDelta1-Fc Enhances IL-10 Production and decreases IFNg and IL-5 Production by Human $CD4^+$ T-Cells



Human CD4+ T-cells stimulated with anti-CD3 + anti-CD28 with or without mouse Delta1-hIgG4 -coated beads

Figure 19: Delta1 enhances IL-10 production by human $CD4^+$ T-cells



Cells stimulated with anti-CD3/CD28 with or without Delta coated beads as shown (medium only and then bead:cell ratios 16:1, 8:1, 4:1, 2:1, 1:1, 0.5:1 and 0.25:1 from left to right in each group)

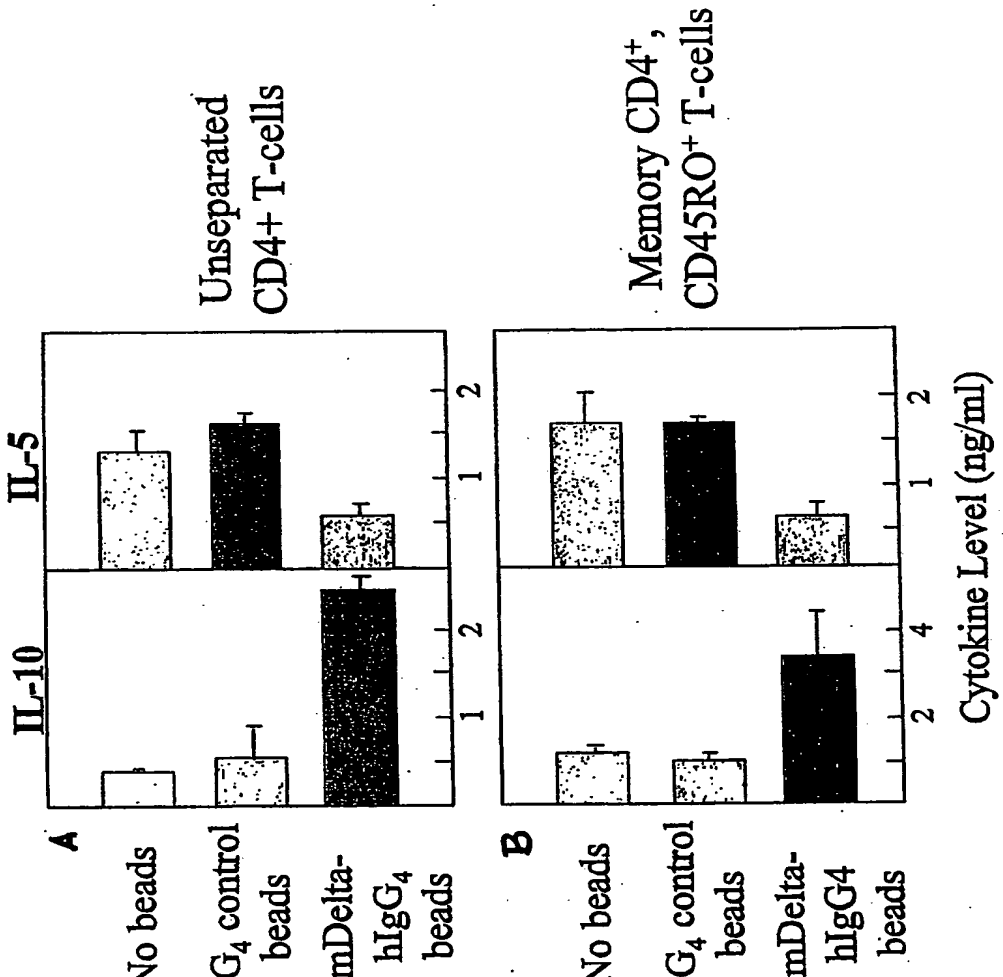


Figure 20: mDelta1-Fc Enhances IL-10 Production and decreases IL-5 production by Anti-CD3/CD28 Activated Human $CD4^+$ T-Cells

Figure 21: Delta-Fc enhances IL-10 production by murine CD4+ T-cells, even in presence of Th1 or Th2 cytokines

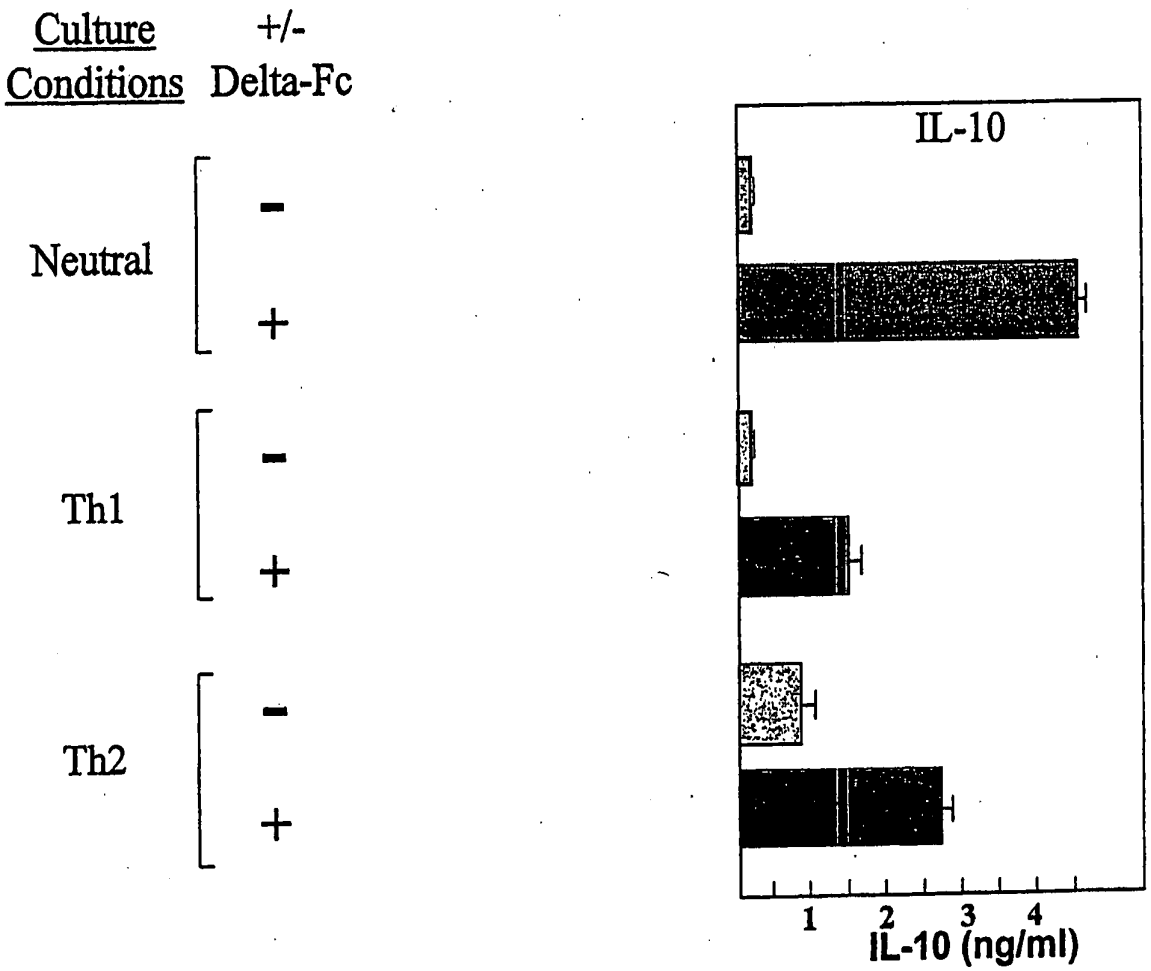


Figure 22: Micro-Array Profiling of Delta-Activated Genes in Jurkat T-Cells

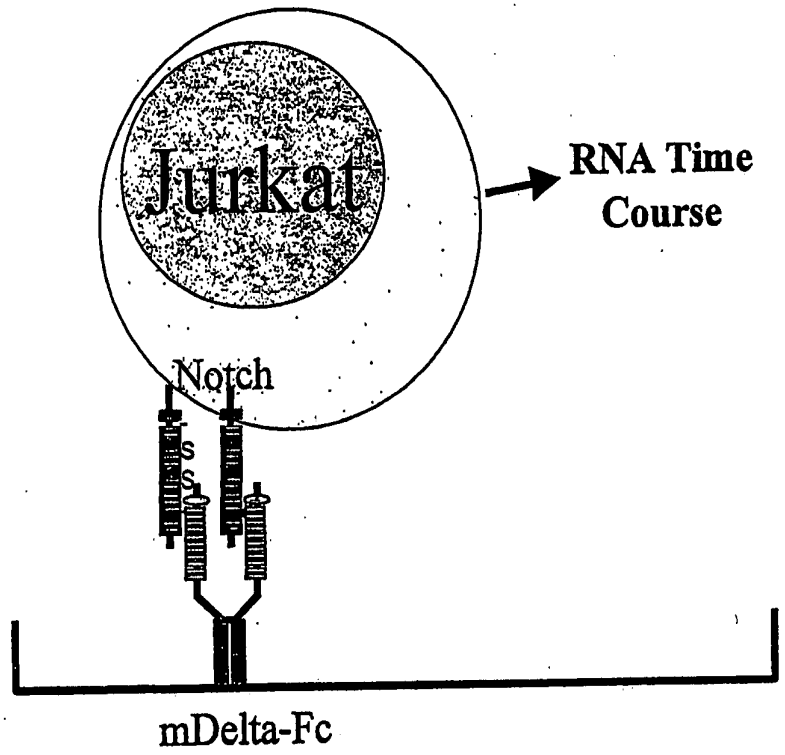


Figure 22A

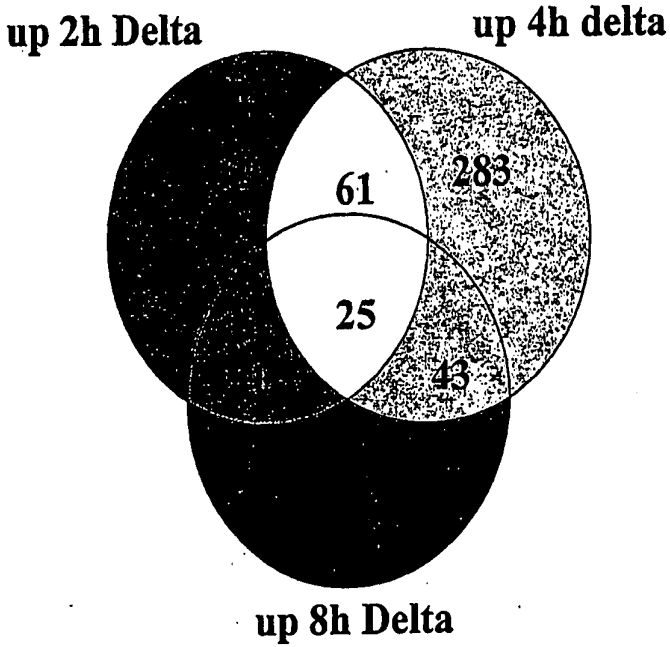


Figure 22B

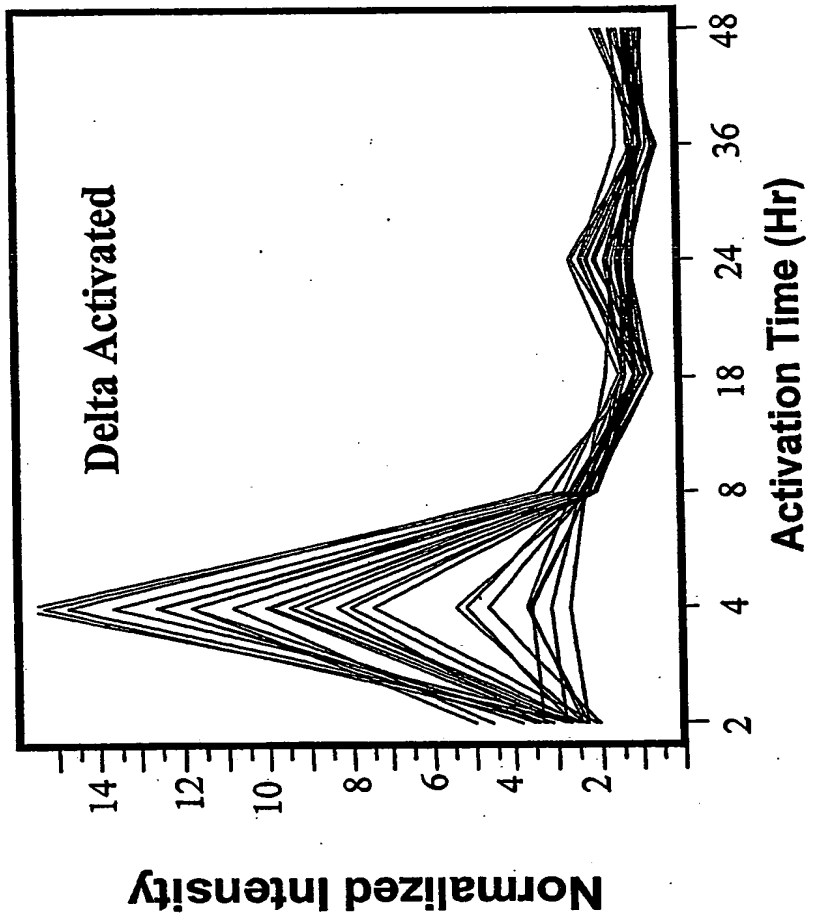


Figure 23: Delta-Mediated Activation of Gene Expression in Jurkat T-Cells

Figure 24: Micro-Array Profiling of Delta-Activated Genes in Jurkat T-Cells

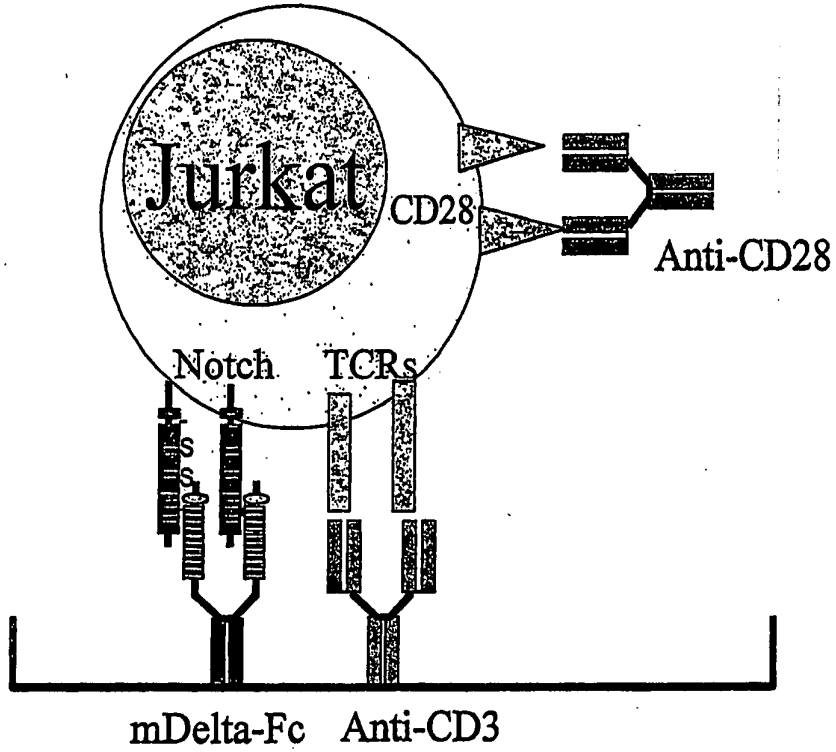


Figure 24A

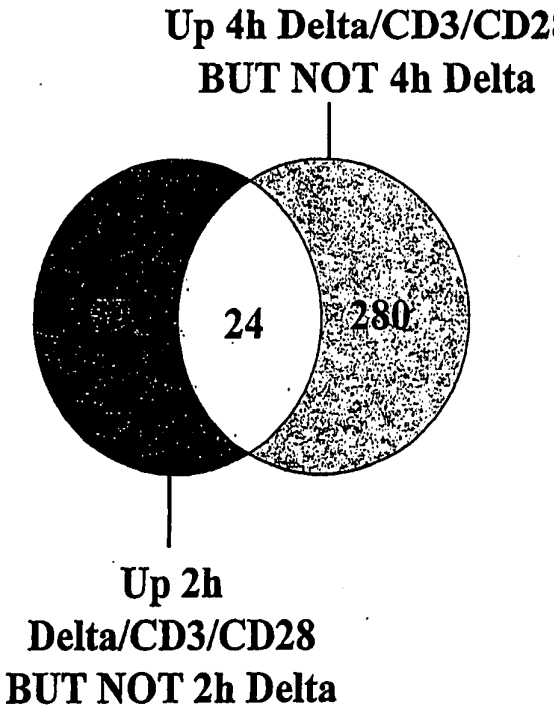
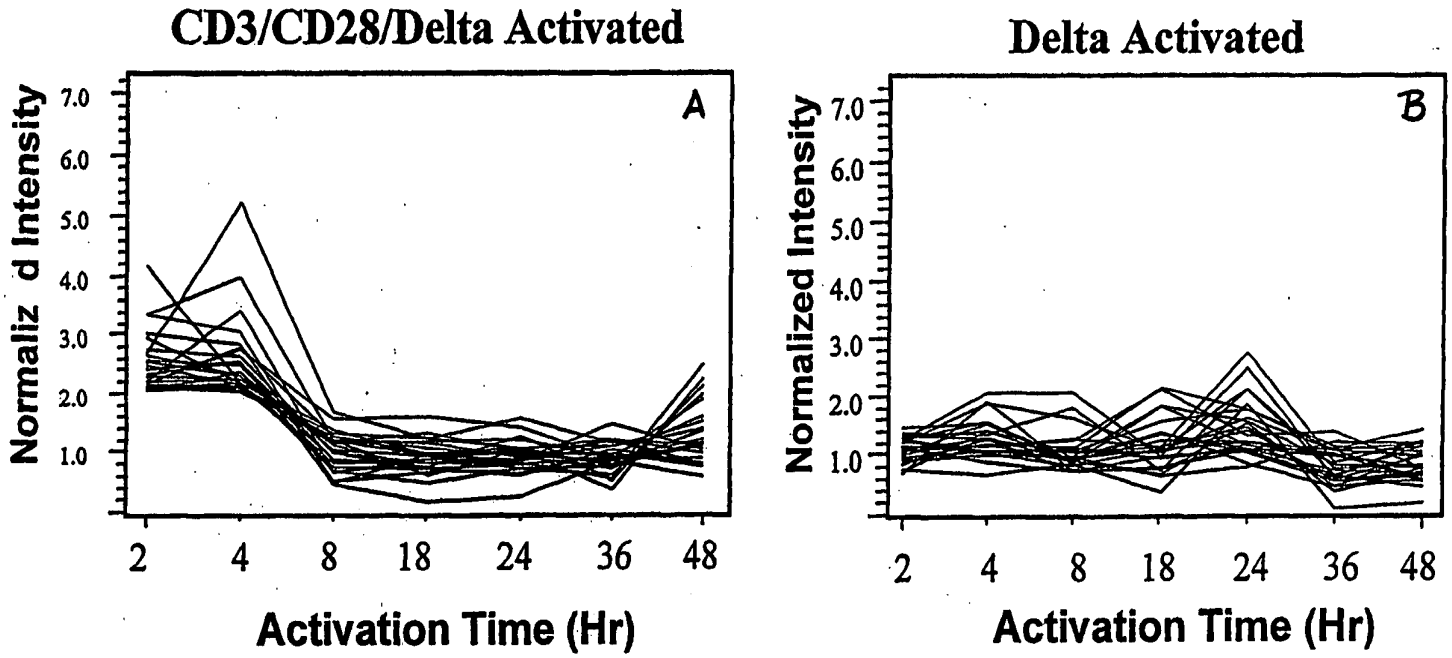


Figure 24B

Figure 25: Delta Modulation of Anti-CD3/CD28 Activation of Gene Expression in Jurkat T-Cells



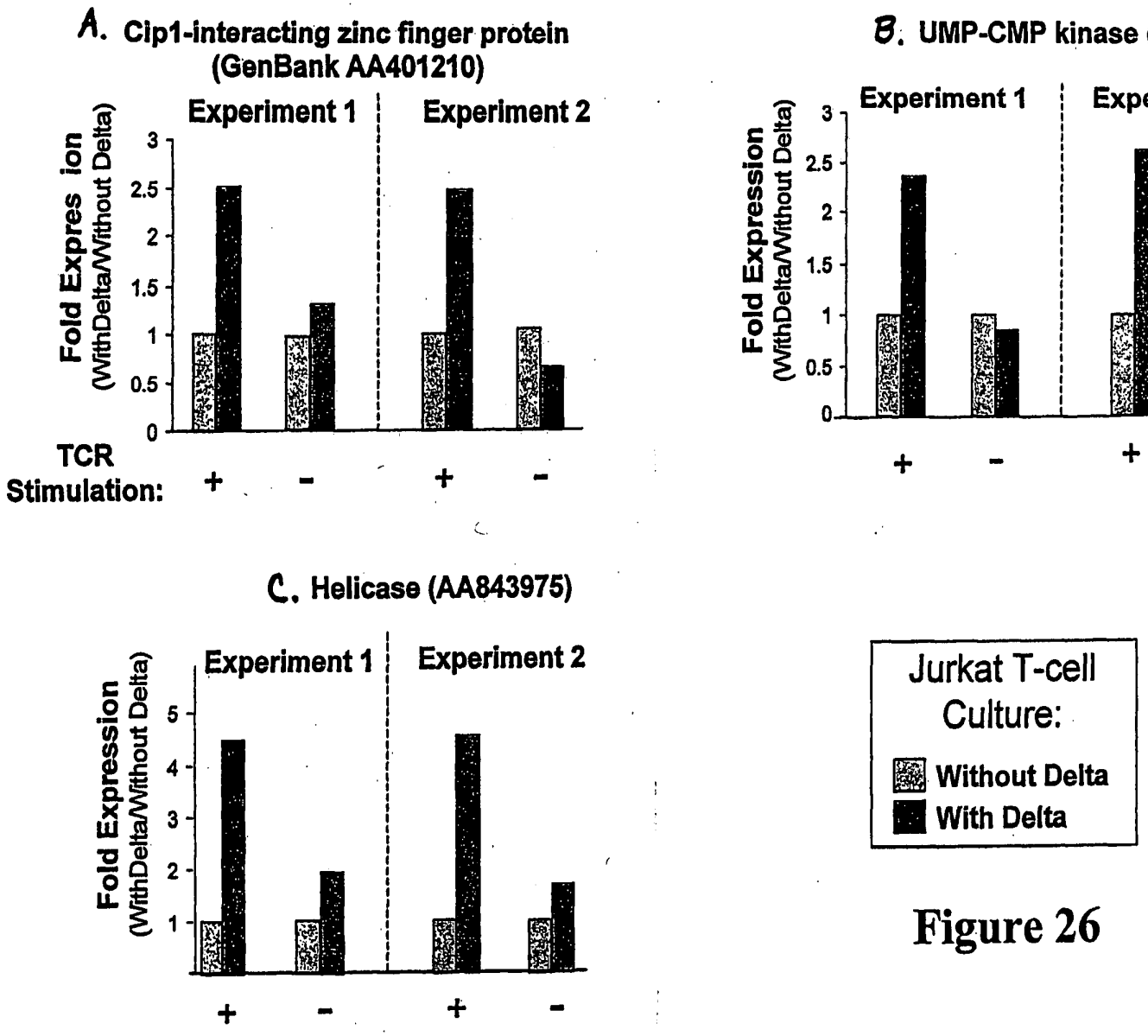

A. Cip1-interacting zinc finger protein (GenBank AA401210)
Experiment 1
Experiment 2
Fold Expres ion (WithDelta/Without Delta)
3
2.5
2
1.5
1
0.5
0
TCR Stimulation:
+
-
+
-
B. UMP-CMP kinase (R66137)
Experiment 1
Experiment 2
Fold Expression (WithDelta/Without Delta)
3
2.5
2
1.5
1
0.5
0
+
-
+
-
C. Helicase (AA843975)
Experiment 1
Experiment 2
Fold Expression (WithDelta/Without Delta)
5
4
3
2
1
+
-
+
-
Jurkat T-cell Culture:
Without Delta
With Delta

Figure 26

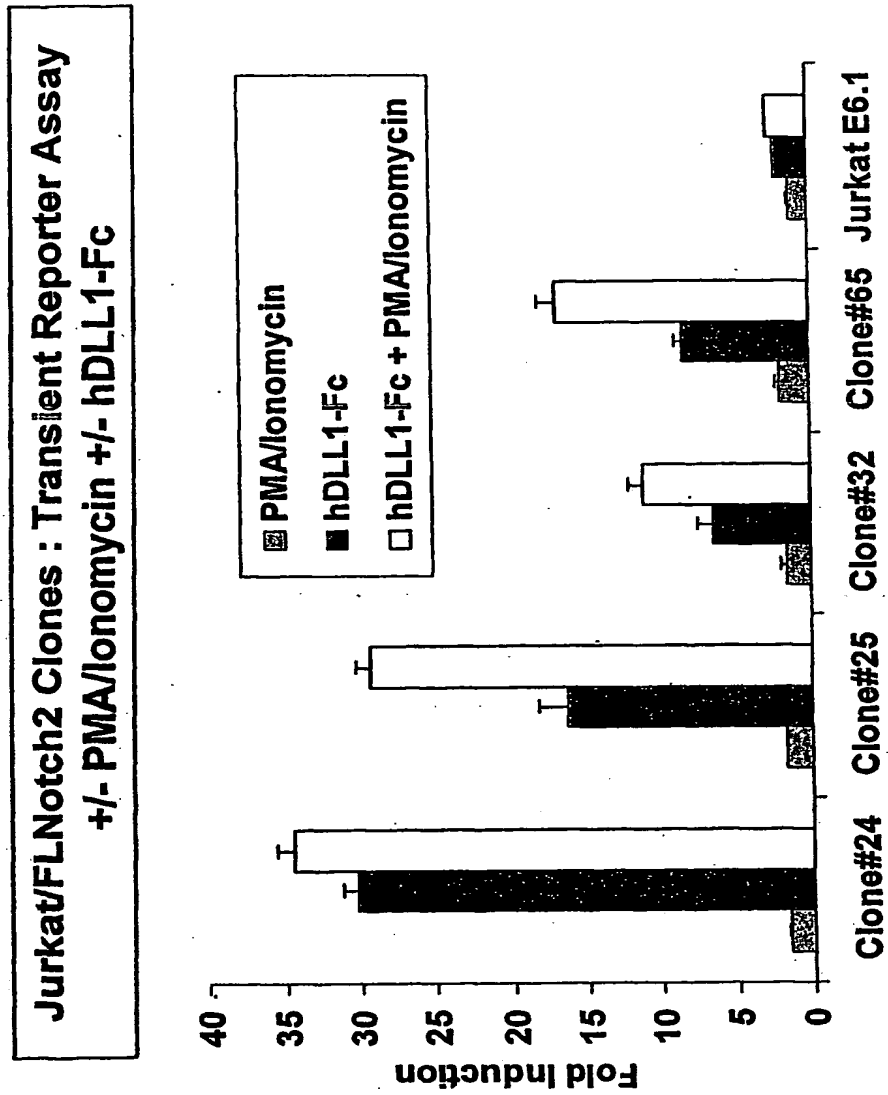

Jurkat/FLNotch2 Clones : Transient Reporter Assay
+/- PMA/Ionomycin +/- hDLL1-Fc
PMA/Ionomycin
hDLL1-Fc
hDLL1-Fc + PMA/Ionomycin
Fold Induction
0
5
10
15
20
25
30
35
40
Clone#24
Clone#25
Clone#32
Clone#65
Jurkat E6.1

Figure 27

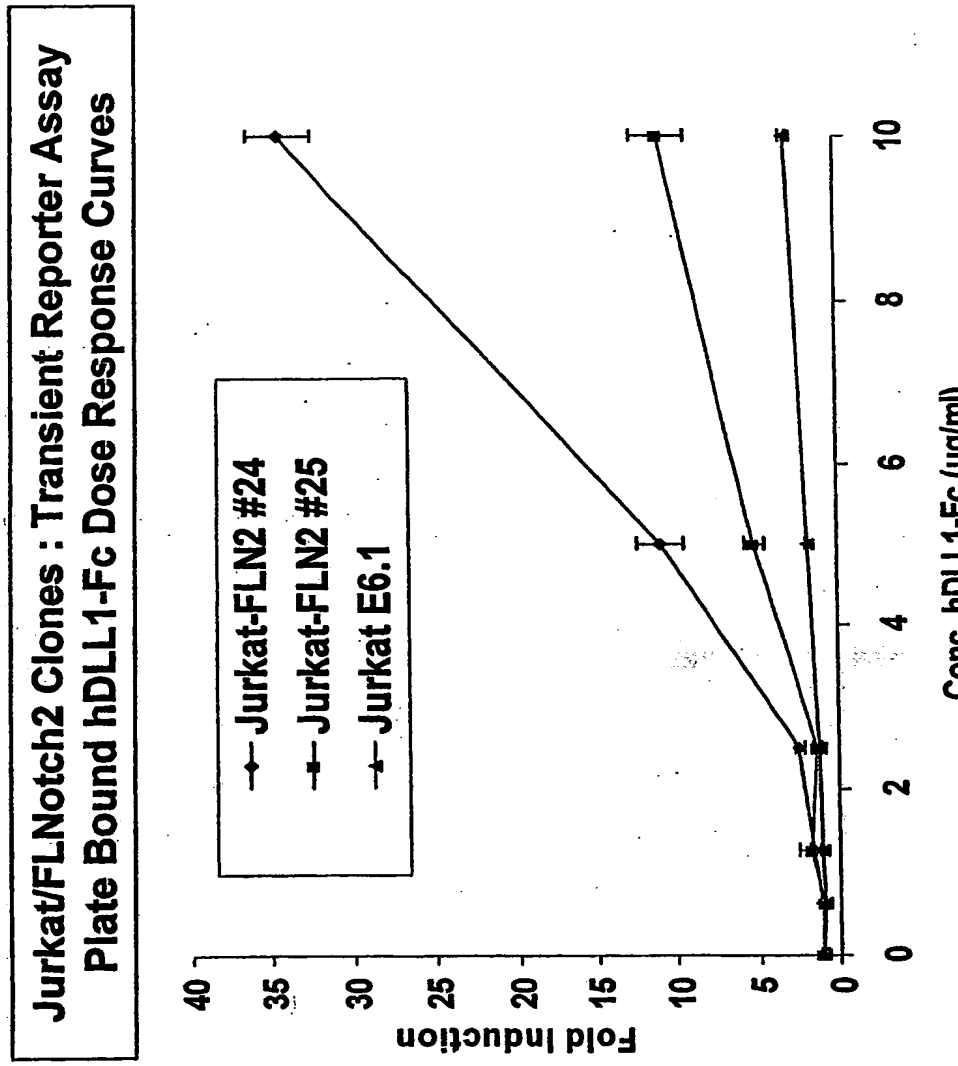

Jurkat/FLNotch2 Clones : Transient Reporter Assay
Plate Bound hDLL1-Fc Dose Response Curves
Jurkat-FLN2 #24
Jurkat-FLN2 #25
Jurkat E6.1
Fold Induction
0
5
10
15
20
25
30
35
40
0
2
4
6
8
10
Conc. hDLL1-Fc (µg/ml)

Figure 28

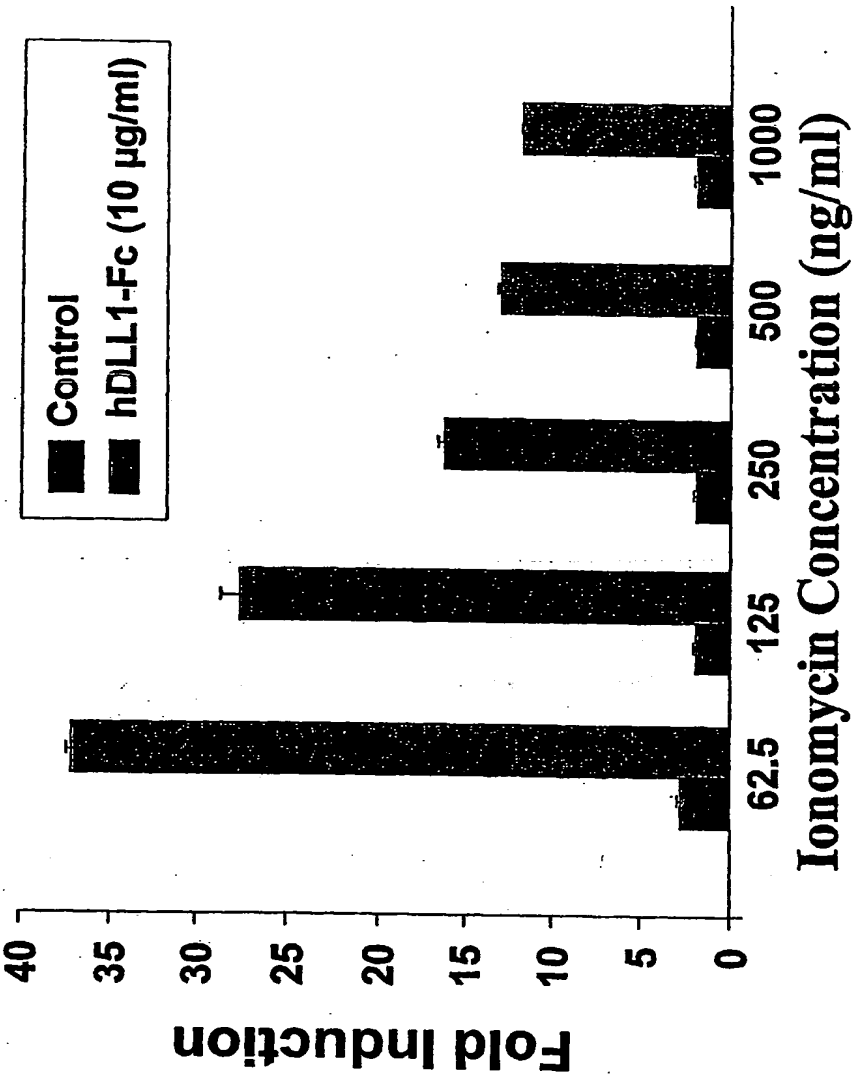
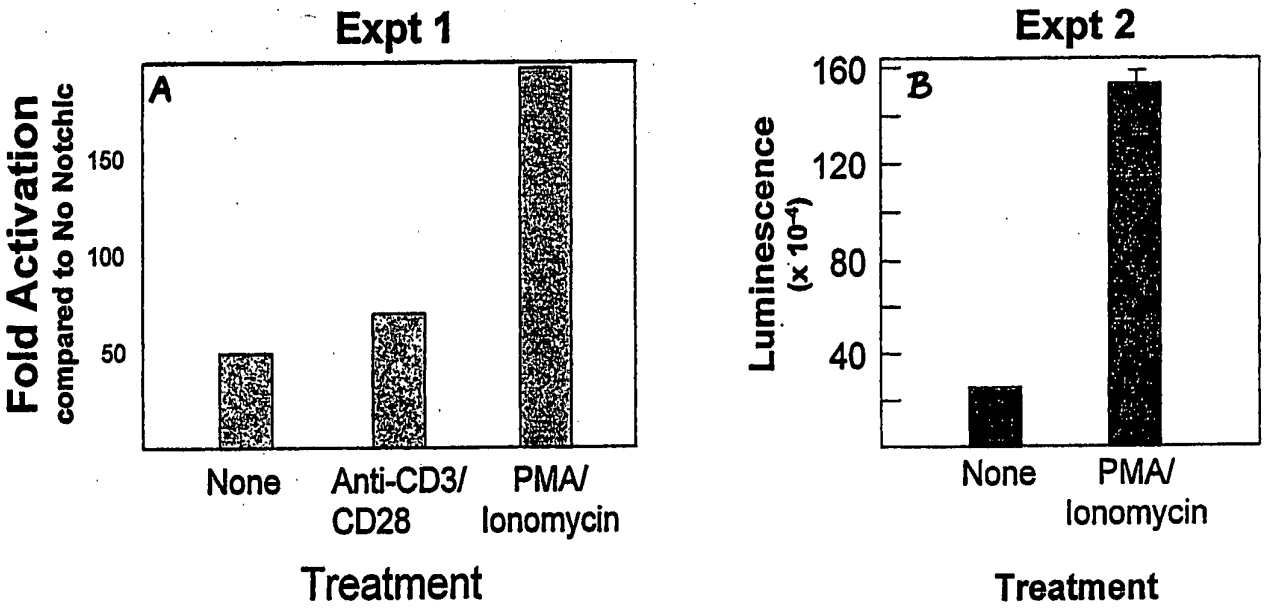

Control
hDLL1-Fc (10 µg/ml)
Fold Induction
0
5
10
15
20
25
30
35
40
62.5
125
250
500
1000
Ionomycin Concentration (ng/ml)

Figure 29



All Cells Transfected with CBF1-luciferase reporter + Nlc

Figure 30

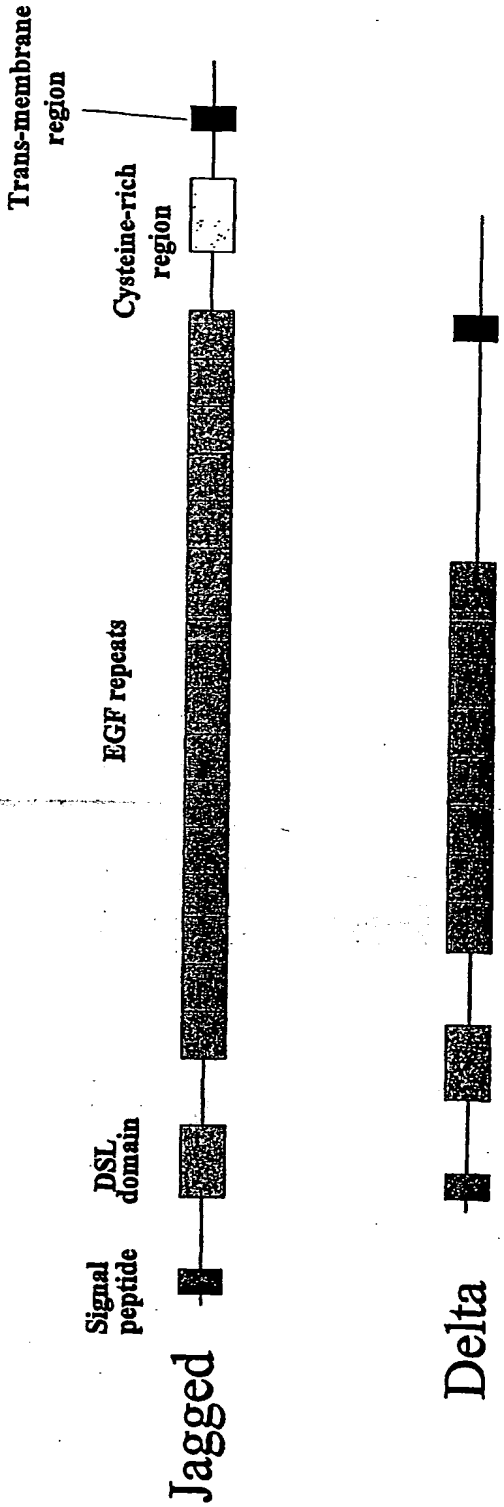

Trans-membrane region
Cysteine-rich region
EGF repeats
DSL domain
Signal peptide
Jagged
Delta

Figure 31

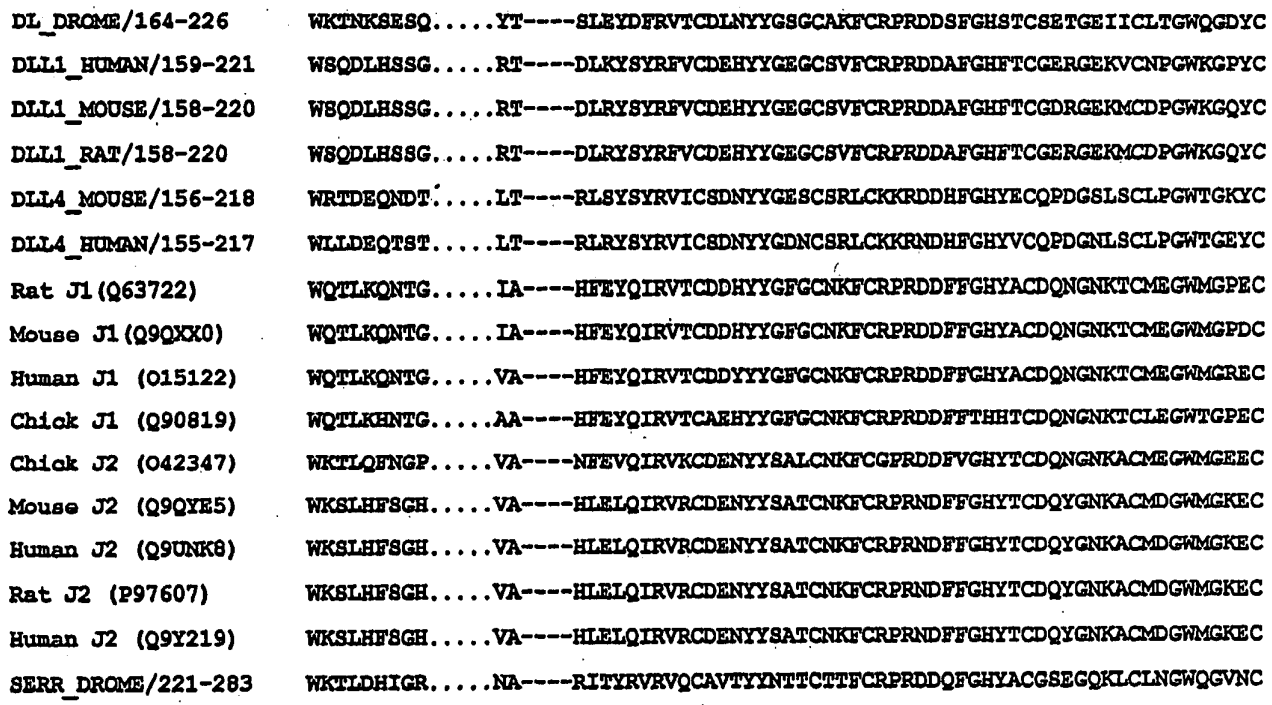

DL_DROME/164-226 WKTNKSESQ.....YT----SLEYDFRVTCDLNYYGSGCAKFCRPRDDSFGHSTCSETGEIICLTGWQGDYC
DLL1_HUMAN/159-221 WSQDLHSSG.....RT----DLKYSYRFVCDEHYYGEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYC
DLL1_MOUSE/158-220 WSQDLHSSG.....RT----DLRYSYRFVCDEHYYGEGCSVFCRPRDDAFGHFTCGDRGEKMCDPGWKGQYC
DLL1_RAT/158-220 WSQDLHSSG.....RT----DLRYSYRFVCDEHYYGEGCSVFCRPRDDAFGHFTCGERGEKMCDPGWKGQYC
DLL4_MOUSE/156-218 WRTDEQNDT.....LT----RLSYSYRVICSDNYYGESCSRLCKKRDDHFGHYECQPDGSLSCLPGWTGKYC
DLL4_HUMAN/155-217 WLLDEQTST.....LT----RLRYSYRVICSDNYYGDNCSRLCKKRNDHFGHYVCQPDGNLSCLPGWTGEYC
Rat J1(Q63722) WQTLKQNTG.....IA----HFEYQIRVTCDDHYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPEC
Mouse J1(Q9QXX0) WQTLKQNTG.....IA----HFEYQIRVTCDDHYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPDC
Human J1 (O15122) WQTLKQNTG.....VA----HFEYQIRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGREC
Chick J1 (Q90819) WQTLKHNTG.....AA----HFEYQIRVTCAEHYYGFGCNKFCRPRDDFFTHHTCDQNGNKTCLEGWTGPEC
Chick J2 (O42347) WKTLQFNGP.....VA----NFEVQIRVKCDENYYSALCNKFCGPRDDFVGHYTCDQNGNKACMEGWMGEEC
Mouse J2 (Q9QYE5) WKSLHFSGH.....VA----HLELQIRVRCDENYYSATCNKFCRPRNDFFGHYTCDQYGNKACMDGWMGKEC
Human J2 (Q9UNK8) WKSLHFSGH.....VA----HLELQIRVRCDENYYSATCNKFCRPRNDFFGHYTCDQYGNKACMDGWMGKEC
Rat J2 (P97607) WKSLHFSGH.....VA----HLELQIRVRCDENYYSATCNKFCRPRNDFFGHYTCDQYGNKACMDGWMGKEC
Human J2 (Q9Y219) WKSLHFSGH.....VA----HLELQIRVRCDENYYSATCNKFCRPRNDFFGHYTCDQYGNKACMDGWMGKEC
SERR_DROME/221-283 WKTLDHIGR.....NA----RITYRVRVQCAVTYYNTTCTTFCRPRDDQFGHYACGSEGQKLCLNGWQGVNC

Figure 32

(human Delta 1; GenBank Accession No. AF003522)

MGSRCALALAVLSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTFFRVCLKHYQASVSPEPPCTYGSAVTPVLGVDSFSLPDGGGA
DSAFSNPIRFPFGFTWPGTFSLIIEALHTDSPDDLATENPERLISRLATQRHLTVGEEWSQDLHSSGRTDLKYSYRFVCDEHYYGEGCSVFCRPRDDAFG
HFTCGERGEKVCNPGWKGPYCTEPICLPGCDEQHGFCDKPGECKCRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCTHHKPCKN
GATCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCTDLENSYSCTCPPGFYGKICELSAMTCADGPCFNGGRCSDSPDGGYSCRCPVGYSGF
NCEKKIDYCSSSPCSNGAKCVDLGDAYLCRCQAGFSGRHCDDNVDDCASSPCANGGTCRDGVNDFSCTCPPGYTGRNCSAPVSRCEHAPCHNGATCHERG
HGYVCECARGYGGPNCQFLLPELPPGPAVVDLTEKLEGQGGPFPWVAVCAGVILVLMLLLGCAAVVVCVRLRLQKHRPPADPCRGETETMNNLANCQREK
DISVSIIGATQIKNTNKKADFHGDHSADKNGFKARYPAVDYNLVQDLKGDDTAVRDAHSKRDTKCQPQGSSGEEKGTPTTLRGGEASERKRPDSGCSTSK
DTKYQSVYVISEEKDECVIATEV

(human Delta 3; GenBank Accession No. NM_016941)

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVCLKPGLSEEAAESPCALGAALSARGPVYTEQPGAPAPDL
PLPDGLLQVPFRDAWPGTFSFIIETWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVGTACTRLCRPRSAPSRCGP
GLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTGPLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRG
FYGLRCEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLCLDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGG
TCVEGGGAHRCSCALGFGGRDCRERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPGDPQRYLLPPALGLLVAAGV
AGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNNLRTQEGSGDGPSSSVDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHL
LFPYPSSILSVK

(human Delta 4; GenBank Accession No. AF 253468)

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCEPGCRTFFRVCLKHFQAVVSPGPCTFGTVSTPVLGTNSFAVRDDSSGGGRN
PLQLPFNFTWPGTFSLIIEAWHAPGDDLRPEALPPDALISKIAIQGSLAVGQNWLLDEQTSTLTRLRYSYRVICSDNYYGDNCSRLCKKRNDHFGHYVCQP
DGNLSCLPGWTGEYCQQPICLSGCHEQNGYCSKPAECLCRPGWQGRLCNECIPHNGCRHGTCSTPWQCTCDEGWGGLFCDQDLNYCTHHSPCKNGATCSNS
GQRSYTCTCRPGYTGVDCELELSECDSNPCRNGGSCKDQEDGYHCLCPPGYYGLHCEHSTLSCADSPCFNGGSCRERNQGANYACECPPNFTGSNCEKKVD
RCTSNPCANGGQCLNRGPSRMCRCRPGFTGTYCELHVSDCARNPCAHGGTCHDLENGLMCTCPAGFSGRRCEVRTSIDACASSPCFNRATCYTDLSTDTFV
CNCPYGFVGSRCEFPVGLPPSFPWVAVSLGVGLAVLLVLLGMVAVAVRQLRLRRPDDGSREAMNNLSDFQKDNLIPAAQLKNTNQKKELEVDCGLDKSNCG
KQQNHTLDYNLAPGPLGRGTMPGKFPHSDKSLGEKAPLRLHSEKPECRISAICSPRDSMYQSVCLISEERNECVIATEV

Figure 33

(human Jagged 1; GenBank Accession No. U73936)

MRSPRTRGRSGRPLSLLLALLCALRAKVCGASGQFELEILSMQNVNGELQNGNCCGGARNPGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSG
STPVIGGNTFNLKASRGNDRNRIVLPFSFAWPRSYTLLVEAWDSSNDTVQPDSIIEKASHSGMINPSRQWQTLKQNTGVAHFEYQIRVTCDDYYYGF
GCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAICRQGCSPKHGSCKLPGDCRCQYGWQGLYCDKCIPHPGCVHGICNEPWQCLCETNWGGQ
LCDKDLNYCGTHQPCLNGGTCSNTGPDKYQCSCPEGYSGPNCEIAEHACLSDPCHNRGSCKETSLGFECECSPGWTGPTCSTNIDDCSPNNCSHGGT
CQDLVNGFKCVCPPQWTGKTCQLDANECEAKPCVNAKSCKNLIASYYCDCLPGWMGQNCDININDCLGQCQNDASCRDLVNGYRCICPPGYAGDHCE
RDIDECASNPCLNGGHCQNEINRFQCLCPTGFSGNLCQLDIDYCEPNPCQNGAQCYNRASDYFCKCPEDYEGKNCSHLKDHCRTTPCEVIDSCTVAM
ASNDTPEGVRYISSNVCGPHGKCKSQSGGKFTCDCNKGFTGTYCHENINDCESNPCRNGGTCIDGVNSYKCICSDGWEGAYCETNINDCSQNPCHNG
GTCRDLVNDFYCDCKNGWKGKTCHSRDSQCDEATCNNGGTCYDEGDAFKCMCPGGWEGTTCNIARNSSCLPNPCHNGGTCVVNGESFTCVCKEGWEG
PICAQNTNDCSPHPCYNSGTCVDGDNWYRCECAPGFAGPDCRININECQSSPCAFGATCVDEINGYRCVCPPGHSGAKCQEVSGRPCITMGSVIPDG
AKWDDDCNTCQCLNGRIACSKVWCGPRPCLLHKGHSECPSGQSCIPILDDQCFVHPCTGVGECRSSSLQPVKTKCTSDSYYQDNCANITFTFNKEMM
SPGLTTEHICSELRNLNILKNVSAEYSIYIACEPSPSANNEIHVAISAEDIRDDGNPIKEITDKIIDLVSKRDGNSSLIAAVAEVRVQRRPLKNRTD
FLVPLLSSVLTVAWICCLVTAFYWCLRKRRKPGSHTHSASEDNTTNNVREQLNQIKNPIEKHGANTVPIKDYENKNSKMSKIRTHNSEVEEDDMDKH
QQKARFAKQPAYTLVDREEKPPNGTPTKHPNWTNKQDNRDLESAQSLNRMEYIV

(human Jagged 2; GenBank Accession No. AF029778)

MRAQGRGRLPRRLLLLLALWVQAARPMGYFELQLSALRNVNGELLSGACCDGDGRTTRAGGCGHDECDTYVRVCLKEYQAKVTPTGPCSYGHGATPV
LGGNSFYLPPAGAAGDRARARARAGGDQDPGLVVIPFQFAWPRSFTLIVEAWDWDNDTTPNEELLIERVSHAGMINPEDRWKSLHFSGHVAHLELQI
RVRCDENYYSATCNKFCRPRNDFFGHYTCDQYGNKACMDGWMGKECKEAVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVPYPGCVHGSCVEPW
QCNCETNWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPCANGGSCHEVPSGFECHCPSGWSGPTCALDIDE
CASNPCAAGGTCVDQVDGFECICPEQWVGATCQLDANECEGKPCLNAFSCKNLIGGYYCDCIPGWKGINCHINVNDCRGQCQHGGTCKDLVNGYQCV
CPRGFGGRHCELERDKCASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVDVDLCEPSPCRNGARCYNLEGDYYCACPDDFGGKNCSVPREPCPGGA
CRVIDGCGSDAGPGMPGTAASGVCGPHGRCVSQPGGNFSCICDSGFTGTYCHENIDDCLGQPCRNGGTCIDEVDAFRCFCPSGWEGELCDTNPNDCL
PDPCHSRGRCYDLVNDFYCACDDGWKGKTCHSREFQCDAYTCSNGGTCYDSGDTFRCACPPGWKGSTCAVAKNSSCLPNPCVNGGTCVGSGASFSCI
CRDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDECQSSPCAYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCW
SRGTPFFPHGSSWVEDCNSCRCLDGRRDCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPPCEAWGECGAEEPPSTPCLPRSGHLDNNC
ARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRASSGASAVEVAVSFSPARDLPDSSLIQGAAHAIVAAITQRGNSSLLLAVTE
VKVETVVTGGSSTGLLVPVLCGAFSVLWLACVVLCVWWTRKRRKERERSRLPREESANNQWAPLNPIRNPIERPGGHKDVLYQCKNFTPPPRRADEA
LPGPAGHAAVREDEEDEDLGRGEEDSLEAEKFLSHKFTKDPGRSPGRPAHWASGPKVDNRAVRSINEARYAGKE

Figure 34

HumanNotch1(AF308602)

MPPLLAPLLCLALLPALAARGPRCSQPGETCLNGGKCEAANGTEACVCGGAFVGPRCQDPNPCLSTPCKNAGTCHVVDRRGVADYACSCALGFSGPLC
LTPLDNACLTNPCRNGGTCDLLTLTEYKCRCPPGWSGKSCQQADPCASNPCANGGQCLPFEASYICHCPPSFHGPTCRQDVNECGQKPRLCRHGGTCH
NEVGSYRCVCRATHTGPNCERPYVPCSPSPCQNGGTCRPTGDVTHECACLPGFTGQNCEENIDDCPGNNCKNGGACVDGVNTYNCPCPPEWTGQYCTE
DVDECQLMPNACQNGGTCHNTHGGYNCVCVNGWTGEDCSENIDDCASAACFHGATCHDRVASFYCECPHGRTGLLCHLNDACISNPCNEGSNCDTNPV
NGKAICTCPSGYTGPACSQDVDECSLGANPCEHAGKCINTLGSFECQCLQGYTGPRCEIDVNECVSNPCQNDATCLDQIGEFQCMCMPGYEGVHCEVN
TDECASSPCLHNGRCLDKINEFQCECPTGFTGHLCQYDVDECASTPCKNGAKCLDGPNTYTCVCTEGYTGTHCEVDIDECDPDPCHYGSCKDGVATFT
CLCRPGYTGHHCETNINECSSQPCRLRGTCQDPDNAYLCFCLKGTTGPNCEINLDDCASSPCDSGTCLDKIDGYECACEPGYTGSMCNSNIDECAGNP
CHNGGTCEDGINGFTCRCPEGYHDPTCLSEVNECNSNPCVHGACRDSLNGYKCDCDPGWSGTNCDINNNECESNPCVNGGTCKDMTSGIVCTCREGFS
GPNCQTNINECASNPCLNKGTCIDDVAGYKCNCLLPYTGATCEVVLAPCAPSPCRNGGECRQSEDYESFSCVCPTAGAKGQTCEVDINECVLSPCRHG
ASCQNTHGXYRCHCQAGYSGRNCETDIDDCRPNPCHNGGSCTDGINTAFCDCLPGFRGTFCEEDINECASDPCRNGANCTDCVDSYTCTCPAGFSGIH
CENNTPDCTESSCFNGGTCVDGINSFTCLCPPGFTGSYCQHVVNECDSRPCLLGGTCQDGRGLHRCTCPQGYTGPNCQNLVHWCDSSPCKNGGKCWQT
HTQYRCECPSGWTGLYCDVPSVSCEVAAQRQGVDVARLCQHGGLCVDAGNTHHCRCQAGYTGSYCEDLVDECSPSPCQNGATCTDYLGGYSCKCVAGY
HGVNCSEEIDECLSHPCQNGGTCLDLPNTYKCSCPRGTQGVHCEINVDDCNPPVDPVSRSPKCFNNGTCVDQVGGYSCTCPPGFVGERCEGDVNECLS
NPCDARGTQNCVQRVNDFHCECRAGHTGRRCESVINGCKGKPCKNGGTCAVASNTARGFICKCPAGFEGATCENDARTCGSLRCLNGGTCISGPRSPT
CLCLGPFTGPECQFPASSPCLGGNPCYNQGTCEPTSESPFYRCLCPAKFNGLLCHILDYSFGGGAGRDIPPPLIEEACELPECQEDAGNKVCSLQCNN
HACGWDGGDCSLNFNDPWKNCTQSLQCWKYFSDGHCDSQCNSAGCLFDGFDCQRAEGQCNPLYDQYCKDHFSDGHCDQGCNSAECEWDGLDCAEHVPE
RLAAGTLVVVVLMPPEQLRNSSFHFLRELSRVLHTNVVFKRDAHGQQMIFPYYGREEELRKHPIKRAAEGWAAPDALLGQVKASLLPGGSEGGRRRRE
LDPMDVRGSIVYLEIDNRQCVQASSQCFQSATDVAAFLGALASLGSLNIPYKIEAVQSETVEPPPPAQLHFMYVAAAAFVLLFFVGCGVLLSRKRRRQ
HGQLWFPEGFKVSEASKKKRREPLGEDSVGLKPLKNASDGALMDDNQNEWGDEDLETKKFRFEEPVVLPDLDDQTDHRQWTQQHLDAADLRMSAMAPT
PPQGEVDADCMDVNVRGPDGFTPLMIASCSGGGLETGNSEEEEDAPAVISDFIYQGASLHNQTDRTGETALHLAARYSRSDAAKRLLEASADANIQDN
MGRTPLHAAVSADAQGVFQILIRNRATDLDARMHDGTTPLILAARLAVEGMLEDLINSHADVNAVDDLGKSALHWAAAVNNVDAAVVLLKNGANKDMQ
NNREETPLFLAAREGSYETAKVLLDHFANRDITDHMDRLPRDIAQERMHHDIVRLLDEYNLVRSPQLHGAPLGGTPTLSPPLCSPNGYLGSLKPGVQG
KKVRKPSSKGLACGSKEAKDLKARRKKSQDGKGCLLDSSGMLSPVDSLESPHGYLSDVASPPLLPSPFQQSPSVPLNHLPGMPDTHLGIGHLNVAAKP
EMAALGGGGRLAFETGPPRLSHLPVASGTSTVLGSSSGGALNFTVGGSTSLNGQCEWLSRLQSGMVPNQYNPLRGSVAPGPLSTQAPSLQHGMVGPLH
SSLAASALSQMMSYQGLPSTRLATQPHLVQTQQVQPQNLQMQQQNLQPANIQQQQSLQPPPPPPQPHLGVSSAASGHLGRSFLSGEPSQADVQPLGPS
SLAVHTILPQESPALPTSLPSSLVPPVTAAQFLTPPSQHSYSSPVDNTPSHQLQVPEHPFLTPSPESPDQWSSSSPHSNVSDWSEGVSSPPTSMQSQI
ARIPEAFK

Figure 35

HumanNotch2(AAA36377)

MPALRPALLWALLALWLCCAAPAHALQCRDGYEPCVNEGMCVTYHNGTGYCKCPEGFLGEYCQHRDPCEKNRCQNGGTCVAQAMLGKATCRCASGF
TGEDCQYSTSHPCFVSRPCLNGGTCHMLSRDTYECTCQVGFTGKECQWTDACLSHPCANGSTCTTVANQFSCKCLTGFTGQKCETDVNECDIPGHC
QHGGTCLNLPGSYQCQCPQGFTGQYCDSLYVPCAPSPCVNGGTCRQTGDFTFECNCLPGFEGSTCERNIDDCPNHRCQNGGVCVDGVNTYNCRCPP
QWTGQFCTEDVDECLLQPNACQNGGTCANRNGGYGCVCVNGWSGDDCSENIDDCAFASCTPGSTCIDRVASFSCMCPEGKAGLLCHLDDACISNPC
HKGALCDTNPLNGQYICTCPQGYKGADCTEDVDECAMANSNPCEHAGKCVNTDGAFHCECLKGYAGPRCEMDINECHSDPCQNDATCLDKIGGFTC
LCMPGFKGVHCELEINECQSNPCVNNGQCVDKVNRFQCLCPPGFTGPVCQIDIDDCSSTPCLNGAKCIDHPNGYECQCATGFTGVLCEENIDNCDP
DPCHHGQCQDGIDSYTCICNPGYMGAICSDQIDECYSSPCLNDGRCIDLVNGYQCNCQPGTSGVNCEINFDDCASNPCIHGICMDGINRYSCVCSP
GFTGQRCNIDIDECASNPCRKGATCINGVNGFRCICPEGPHHPSCYSQVNECLSNPCIHGNCTGGLSGYKCLCDAGWVGINCEVDKNECLSNPCQN
GGTCDNLVNGYRCTCKKGFKGYNCQVNIDECASNPCLNQGTCFDDISGYTCHCVLPYTGKNCQTVLAPCSPNPCENAAVCKESPNFESYTCLCAPG
WQGQRCTIDIDECISKPCMNHGLCHNTQGSYMCECPPGFSGMDCEEDIDDCLANPCQNGGSCMDGVNTFSCLCLPGFTGDKCQTDMNECLSEPCKN
GGTCSDYVNSYTCKCQAGFDGVHCENNINECTESSCFNGGTCVDGINSFSCLCPVGFTGSFCLHEINECSSHPCLNEGTCVDGLGTYRCSCPLGYT
GKNCQTLVNLCSRSPCKNKGTCVQKKAESQCLCPSGWAGAYCDVPNVSCDIAASRRGVLVEHLCQHSGVCINAGNTHYCQCPLGYTGSYCEEQLDE
CASNPCQHGATCSDFIGGYRCECVPGYQGVNCEYEVDECQNQPCQNGGTCIDLVNHFKCSCPPGTRGLLCEENIDDCARGPHCLNGGQCMDRIGGY
SCRCLPGFAGERCEGDINECLSNPCSSEGSLDCIQLTNDYLCVCRSAFTGRHCETFVDVCPQMPCLNGGTCAVASNMPDGFICRCPPGFSGARCQS
SCGQVKCRKGEQCVHTASGPRCFCPSPRDCESGCASSPCQHGGSCHPQRQPPYYSCQCAPPFSGSRCELYTAPPSTPPATCLSQYCADKARDGVCD
EACNSHACQWDGGDCSLTMENPWANCSSPLPCWDYINNQCDELCNTVECLFDNFECQGNSKTCKYDKYCADHFKDNHCNQGCNSEECGWDGLDCAA
DQPENLAEGTLVIVVLMPPEQLLQDARSFLRALGTLLHTNLRIKRDSQGELMVYPYYGEKSAAMKKQRMTRRSLPGEQEQEVAGSKVFLEIDNRQC
VQDSDHCFKNTDAAAALLASHAIQGTLSYPLVSVVSESLTPERTQLLYLLAVAVVIILFIILLGVIMAKRKRKHGSLWLPEGFTLRRDASNHKRRE
PVGQDAVGLKNLSVQVSEANLIGTGTSEHWVDDEGPQPKKVKAEDEALLSEEDDPIDRRPWTQQHLEAADIRRTPSLALTPPQAEQEVDVLDVNVR
GPDGCTPIMLASLRGGSSDLSDEDEDAEDSSANIITDLVYQGASLQAQTDRTGEMALHLAARYSRADAAKRLLDAGADANAQDNMGRCPLHAAVAA
DAQGVFQILIRNRVTDLDARMNDGTTPLILAARLAVEGMVAELINCQADVNAVDDHGKSALHWAAAVNNVEATLLLLKNGANRDMQDNKEETPLFL
AAREGSYEAAKILLDHFANRDITDHMDRLPRDVARDRMHHDIVRLLDEYNVTPSPPGTVLTSALSPVICGPNRSFLSLKHTPMGKKSRRPSAKSTM
PTSLPNLAKEAKDAKGSRRKKSLSEKVQLSESSVTLSPVDSLESPHTYVSDTTSSPMITSPGILQASPNPMLATAAPPAPVHAQHALSFSNLHEMQ
PLAHGASTVLPSVSQLLSHHHIVSPGSGSAGSLSRLHPVPVPADWMNRMEVNETQYNEMFGMVLAPAEGTHPGIAPQSRPPEGKHITTPREPLPPI
VTFQLIPKGSIAQPAGAPQPQSTCPPAVAGPLPTMYQIPEMARLPSVAFPTAMMPQQDGQVAQTILPAYHPFPASVGKYPTPPSQHSYASSNAAER
TPSHSGHLQGEHPYLTPSPESPDQWSSSSPHSASDWSDVTTSPTPGGAGGQRGPGTHMSEPPHNNMQVYA

Figure 36

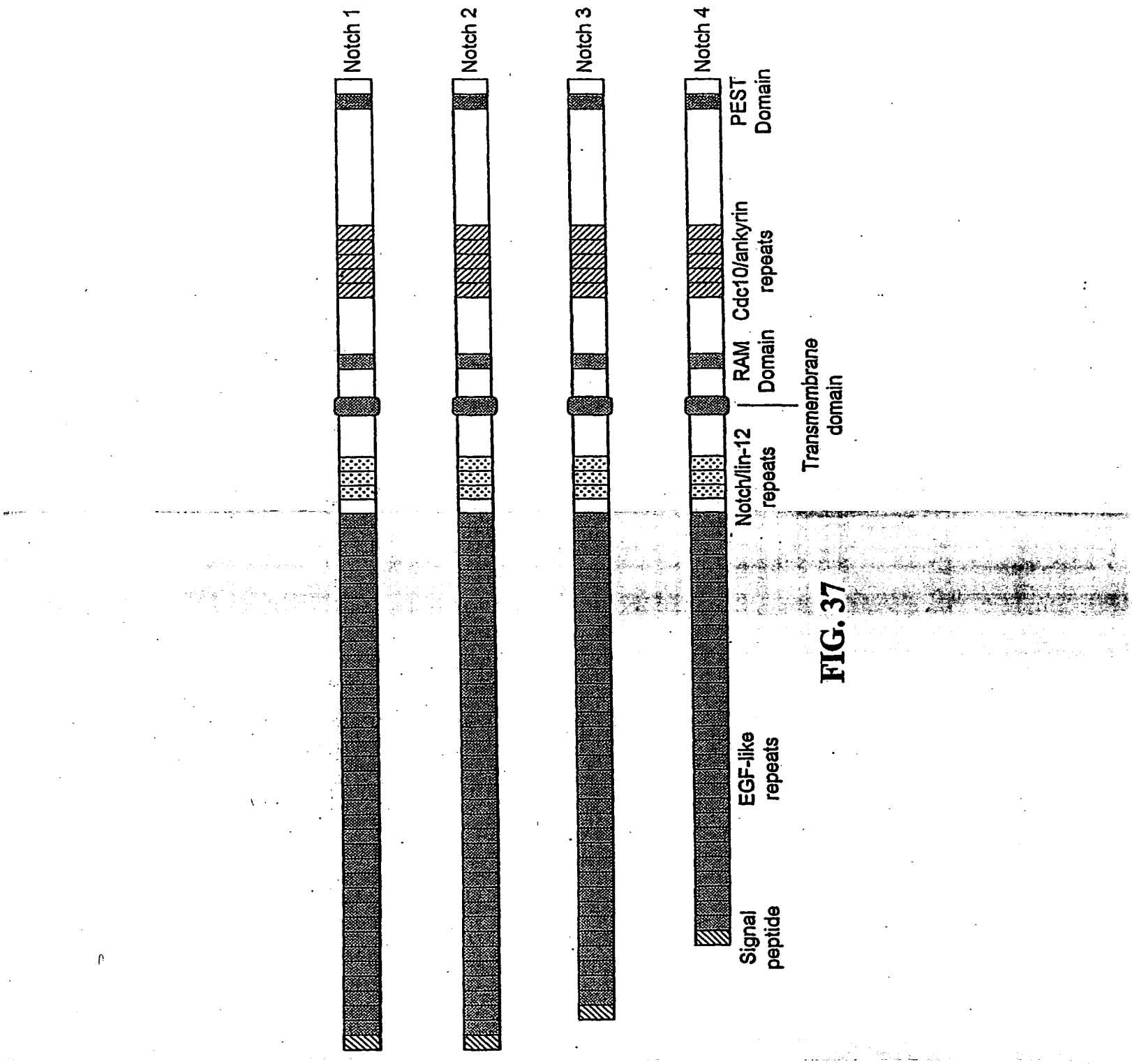

Notch 1
Notch 2
Notch 3
Notch 4
PEST Domain
RAM Domain
Cdc10/ankyrin repeats
Transmembrane domain
Notch/lin-12 repeats
EGF-like repeats
Signal peptide

FIG. 37

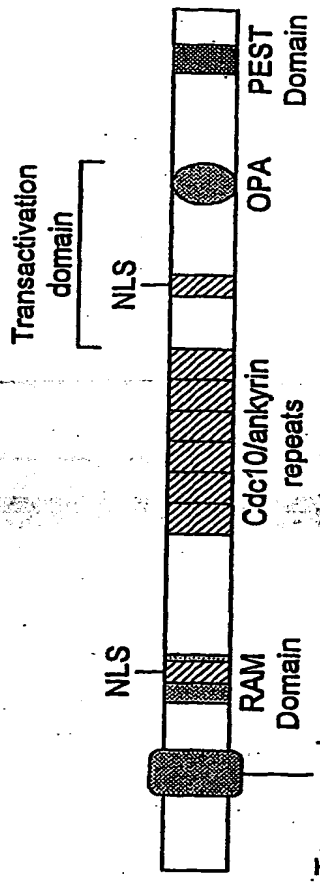

Transactivation domain
NLS
OPA
PEST Domain
Cdc10/ankyrin repeats
NLS
RAM Domain
Transmembrane domain

FIG. 38